

APPLICATION FOR UNITED STATES LETTERS PATENT

Applicants: Klaus Gassenmeier
Willi Grab
Christophe Galopin
Beatrice Bigler

Title: ORGANOLEPTIC COMPOSITIONS: USE OF 3-MERCAPTO
ALKANOIC ACID ESTERS AS FLAVOR INGREDIENTS

Assignee: Givaudan SA

Beverly A. Lyman
WOOD, HERRON & EVANS, L.L.P.
2700 Carew Tower
Cincinnati OH 45202
(513) 241-2324
(513) 421-7269 (Facsimile)

SPECIFICATION

**ORGANOLEPTIC COMPOSITIONS: USE OF 3-MERCAPTO
ALKANOIC ACID ESTERS AS FLAVOR INGREDIENTS**

This application claims the benefit of European Application
Serial No. 104904.8, filed March 8, 2000.

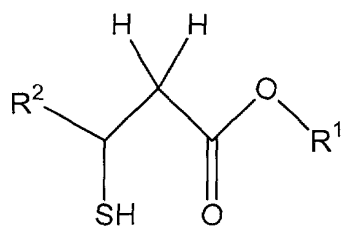
5 **Field of the Invention**

The present invention relates to flavor or fragrance
compositions comprising 3-mercapto carboxylic esters and/or precursors
thereof, and to a method of flavoring a food, a beverage or a consumer
healthcare or household product using these compounds.

10 **Background of the Invention**

Swiss patent 557 423 describes 3-mercapto carboxylic esters
of the general formula I

-2-

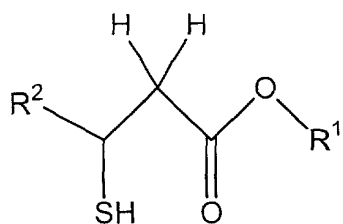


wherein R¹ represents an alkyl or alkenyl or alkadienyl group with 1 to 6 carbon atoms, and R² represents an alkyl or alkenyl group containing 3 to 9 carbon atoms. These 3-mercapto carboxylic esters are known as flavor or fragrance compounds, and possess either green organoleptic properties, e.g. leaf green (3-mercapto-4-methylhexanoic acid ethyl ester), green fruity (3-mercapto-4-methylhexanoic acid hex-3-enyl ester), green and pungent (3-mercapto-4-methylhexanoic acid 2-hexenyl ester), or fatty organoleptic properties (e.g. 3-mercaptooctanoic acid ethyl ester, 3-mercaptodecanoic acid ethyl ester, 3-mercaptododecanoic acid ethyl ester or 3-mercapto-4-ethylhexanoic acid ethyl ester). An exception is 3-mercapto-4-methylhexanoic acid hexa-2,4-dienyl ester with a sulfurous, onion and garlic-like note. The latter-mentioned compound demonstrates that a small change in the structure of the compound can cause a dramatic change of the odor properties; e.g. a hexa-2,4-dienyl group instead of a hex-3-enyl group changes the organoleptic character from green-fruity to onion, garlic-like.

The flavor and fragrance industry is further interested in new ingredients with a clear fruity character. Thus, the above mentioned compounds would be of interest if they do not have the disadvantage that the fruity note is always combined with green and/or fatty notes.

5 Summary of the Invention

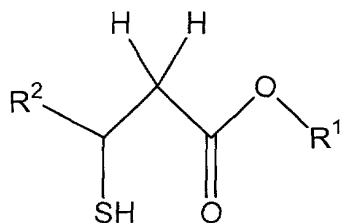
The invention is directed to a flavor or fragrance composition having at least one compound of formula I



or a precursor thereof, wherein R1 represents a branched or unbranched alkyl, alkenyl or alkadienyl group containing 1 to 8 carbon atoms and R2 represents a methyl or ethyl group. In one embodiment, R1 may be methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-hexyl, (Z)-2-hexenyl, (E)-3-hexenyl, (E)-2-hexenyl, (Z)-3-hexenyl or n-octyl. The compound in the composition may be 3-mercaptopentanoic acid methyl ester, 3-mercaptopentanoic acid ethyl ester, 3-mercaptopentanoic acid n-hexyl ester, (R)-3-mercaptopentanoic acid methyl ester, 3-mercaptopentanoic acid (Z)-3-hexenyl ester, 3-mercaptopentanoic acid ethyl ester. Precursors of these

compounds may also be used, such as where the precursor is formed by reacting acyl chloride with the compound of formula 1. The concentration of the compound of formula 1 or the precursor in the composition is from 0.001% to 30%.

5 The invention is also directed to a method of adding a flavor or fragrance to a product by adding to the product at least one compound of formula 1

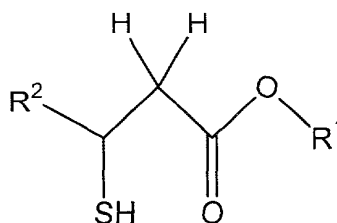


or a precursor, wherein R¹ represents a branched or unbranched alkyl, alkenyl or alkadienyl group containing 1 to 8 carbon atoms and R² represents a methyl or an ethyl group. The product may be a food, beverage, healthcare product, and/or a household product. In one embodiment, R¹ is selected from the group consisting of methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-hexyl, (Z)-2-hexenyl, (E)-3-hexenyl, (E)-2-hexenyl, (Z)-3-hexenyl and n-octyl. The compound may be 3-mercaptoputanoic acid methyl ester, 3-mercaptoputanoic acid ethyl ester, 3-mercaptoputanoic acid n-hexyl ester, (R)-3-mercaptoputanoic acid

methyl ester, 3-mercaptobutanoic acid (Z)-3-hexenyl ester, 3-mercaptopentanoic acid ethyl ester, or precursors of these compounds. The compound(s) of formula I or the precursor(s) thereof is/are present in an amount of 0.001 mg/kg to 500 mg/kg of the product.

5 **Detailed Description**

Surprisingly, it has now been found that compounds of formula I



and precursors thereof, wherein R¹ represents an alkyl, alkenyl or alkadienyl group containing 1 to 8 carbon atoms and R² represents a methyl or an ethyl group, whereby the alkyl, alkenyl or alkadienyl group can be branched or unbranched, overcome the afore mentioned disadvantage of having the fruity note always combined with green and/or fatty notes, and, hence, can be used as flavor or fragrance compounds with a clear fresh character. Thus, the present invention is directed to this subject matter. The compounds according to the invention can advantageously be used as ingredients for flavor or fragrance compositions as will be explained below. If the

compounds contain double bonds, they can exist in any desired stereoconfiguration.

Preferred examples of R1 are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-hexyl, (Z)-2-hexenyl, (E)-3-hexenyl, (E)-2-hexenyl, (Z)-3-hexenyl and n-octyl.

The compounds include the racemates as well as the pure enantiomers, which are defined by the asymmetric center in beta position to the acid functionality.

Especially preferred compounds to be used as flavor or fragrance ingredients are 3-mercaptoputanoic acid methyl ester, 3-mercaptoputanoic acid ethyl ester, 3-mercaptoputanoic acid n-hexyl ester, (R)-3-mercaptoputanoic acid methyl ester, 3-mercaptoputanoic acid (Z)-3-hexenyl ester and 3-mercaptopentanoic acid ethyl ester, whereby 3-mercaptoputanoic acid methyl ester and 3-mercaptoputanoic acid ethyl ester are most preferred.

Structurally, the compounds according to the invention differ from the compounds described in the afore mentioned Swiss patent 557 423 in their chain length of the acid.

3-mercaptoalkanoic acid esters according to the present invention are known in the literature, e.g. by the German Offenlegungsschrift 2 363 573. They are, for example, used as intermediates in the synthesis of pharmaceuticals (e.g. leukotriene antagonists and inhibitors of leukotriene biosynthesis as described by the European patent publication EP 0399818). Further, US patent 3,954,843 describes the general synthetic pathways for the production of the racemates, and in Tetrahedron Letters, Vol 32, No. 46, pp 6723-6726, 1991, the production of the pure enantiomer is described.

It has been found that the compounds of the present invention exhibit fruity properties, mainly in the range of passion fruit, cassis or tropical fruit. These organoleptic properties have never been described before, although the compounds themselves are already known, as previously stated. They differ strongly in their organoleptic properties from the compounds mentioned in Swiss patent 557 423, and the unwanted, disturbing green or fatty odor aspects are absent.

The preferred compounds according to the invention are the short chain compounds with a total maximum number of 7 carbon atoms. They exhibit strong cassis-like and/or red fruit notes, which remind on passion fruit, black current and blackberry.

Compounds according to the invention with a total carbon atom number of equal to or greater than 8 are very substantive and, therefore, are specifically useful as ingredients in fragrances. They exhibit fresh-cassis and ripe-estery notes, and remind on grapefruit and/or citrus and/or Riesling wine.

5 It was found that the organoleptic properties of the R and S isomers are very similar. Therefore, from the economic point of view, the easier and cheaper accessible racemates are preferred over the pure enantiomers.

10 Based on their clear fruity organoleptic properties, the compounds are suitable for the creation of flavor and fragrance compositions. They can be combined in the usual manner with practically all available flavor or fragrance raw materials, i.e. synthetic and/or nature identical and/or natural substances and/or natural extracts and/or additional carrier materials and/or further additives used in the flavor or fragrance field.

15 Specifically, the very distinct berry and estery floral notes of the compounds according to the invention enable the production of specific and characteristic flavor profiles, which are new. These can be used for the aromatization of foodstuffs, beverages, pharmaceuticals, oral hygiene products (e.g. toothpaste) or other healthcare products.

Further, specifically the compounds of the invention add a berry, fruity and some tropical aspects to fruit flavor compositions such as peach, strawberry, passion fruit, citrus and raspberry. Thereby the body of the flavor is increased and its stability (longevity) improved. However, use is not restricted to fruit flavors, as the inventive compounds can also be combined also with herbal, mint and savory flavors, whereby they especially increase the fullness, freshness and/or the herbal character. For example, in meat flavors, they increase the natural meat aroma.

Due to their fruity odor characteristics, the compounds of the invention can also be used in fragrance compositions such as fine fragrances or perfumed products of all kinds, especially cosmetic articles, consumer healthcare or household products as, e.g., washing agents, detergents, soaps or toothpaste. Here, specifically, the inventive compounds add an herbal-fruity and, surprisingly, also a marine aspect to floral, musk and woody accords. At the same time the freshness is increased.

The preferred dosage range of the compounds according to the invention in a food, a beverage, a consumer healthcare or a household product is from 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 50 mg/kg. In fragrance compositions, concentrations of the inventive

compound(s) from 0.001% to 30%, preferably from 0.01% to 10%, are preferably used.

Instead of directly using a compound of the invention as a flavor or fragrance ingredient, it may be advantageous to use a precursor thereof, i.e. a chemical derivative of a compound according to the invention which can be easily transformed to the compound according to the invention. The precursors themselves can already be of sensorial interest. For example, and preferably, as precursors the esters of 3-acylthio acids, which can be obtained by treatment of the compounds according to the invention with acyl chloride, may be added to an aroma or food or fragrance composition. From the esters of 3-acylthioacids, the inventive compounds can be released by enzymatic hydrolysis and/or chemical treatment. This reaction can take place either in the flavor or fragrance composition, or in the products containing these compositions.

The present invention is described further in the following examples, which are presented solely for the non-limiting purpose of further illustrating the invention.

EXAMPLE 1

Synthesis of 3-mercaptopentanoic acid methyl ester

At 0°C, 5.71 g of 2-pentenoic acid methyl ester was introduced in a 500 mL round-bottom flask containing 200 mL of dry methanol. A solution of 4.44 g of NaSH·H₂O and 2.57 mL acetic acid in 100 mL methanol was then added. The resulting orange mixture was stirred at room temperature for two days. The solution was then concentrated, taken in ether, washed with water, dried over MgSO₄, filtered and concentrated again. This gave seven grams of a pale yellow oil containing about 38% of the desired compound, which was purified by column chromatography.

EXAMPLE 2

Synthesis of (R)-3-mercaptoputanoic acid methyl ester

The synthesis was done according to the description of Breitschuh, R. and Seebach, D.; *Synthesis*, 1992, 83-89 as follows:

At 0°C, 82.31 g of NaSH·H₂O was added to a 1.5 L round-bottom flask containing 600 mL of distilled water. To this solution, 83.08 g of (S)-b-butyrolactone was added over a period of 20 minutes. The mixture was stirred for 1 h at 0°C and remained overnight at room temperature. The solution was then brought to pH 2 and was extracted with ether. The

organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated to give 110 g of slightly yellow oil. In a 250 mL flask, 30 g of the oil previously obtained was dissolved in 80 mL of methanol. A catalytic amount of sulfuric acid was added to the mixture, which was heated at reflux for 19 h. The solution was then concentrated and partitioned between ether and cold brine. The organic layer was washed with sodium bicarbonate and brine, dried over MgSO_4 , filtered, and concentrated. The result was 35.2 g of oil, which was purified by chromatography on silica gel.

EXAMPLE 3

10 Synthesis of 3-acetylthiobutanoic acid hexyl ester

At room temperature, in a 250 mL round-bottom flask with a gas outlet, 21 g of 3-mercaptopbutanoic acid hexyl ester was dissolved in 50 mL of neat acetyl chloride. The mixture was stirred at room temperature for 6 h. It was then cooled to 0°C and the reaction was quenched by careful addition of 100 mL of dry methanol in small portions. The mixture was then washed with bicarbonate, dried over MgSO_4 , filtered, and concentrated, and gave the acetylated compound in 98% yield.

Example 4

To a tropical fruit soft drink of the following composition (a), containing the following fruit flavor (b), 0.1 mg/L 3-mercaptoputanoic acid methyl ester was added.

5 (a) Composition of typical tropical fruit soft drink:

		[g]
	water	9500
	sugar syrup 65 Brix	170
	citric acid 50%	5
10	sodium citrate	0.4
	sodium benzoate	0.15
	tropical fruit flavor (b)	0.3

(b) Composition of tropical fruit flavor:

		[g]
15	benzaldehyde	4.0
	linalool	4.0
	(Z)-3-hexenyl butanoate	4.0
	4-hydroxy-2,5-dimethyl- 2(5H)-dihydrofuran-3-one	8.0
20	ethyl butanoate	30.0
	hexyl butanoate	24.0
	ethyl hexanoate	14.0
	1-phenylethyl acetate	9.8
	3,7-dimethyl-2,6-octadienthiol	0.2
25	(Z)-3-hexenol	2.0
	propylenglycol	900.0

Compared with the aroma note of the starting soft drink, additionally a passion fruit typical top note occurred and, at the same time, the freshness was increased significantly.

EXAMPLE 5

5 To an orange soft drink (blank) of the composition as described below, and having an orange, aldehydic and soapy aroma, was added 3-mercaptoputanoic acid methyl ester, on one hand and, on the other hand, 3-mercaptoputanoic acid methyl ester. 3-mercaptoputanoic acid methyl ester is an example from the group of compounds described by Swiss patent 10 557 423 and having a structure closest to the compound of the present invention. Each of 3-mercaptoputanoic acid methyl ester and 3-mercaptoputanoic acid methyl ester was added at a level of 0.1 mg/L, and each was compared with the blank orange soft drink.

Composition of orange soft drink:

15		[g]
	water	9500
	sugar syrup 65 Brix	170
	citric acid 50%	5
	sodium citrate	0.4
20	sodium benzoate	0.15
	orange oil 40 fold	0.005

The drink containing 3-mercaptoputanoic acid methyl ester exhibited an orange, mandarin, fresh squeezed juice note with strong fruity aspects, which is a significant improvement over the blank soft drink. In contrast, the drink containing 3-mercaptoputanoic acid methyl ester exhibited a strong fatty sulfury-woody aroma with a grapefruit aspect.

EXAMPLE 6

To a woodberry flavored yogurt (blank) consisting of components (a) and (b) as described below, 3-mercaptoputanoic acid methyl ester and 3-mercaptoputanoic acid ethyl ester were added. These were compared with a yogurt to which 3-mercaptoputanoic acid methyl ester was added. To the blank woodberry flavored yogurt 0.2 mg/kg of 3-mercaptoputanoic acid methyl ester was added.

- (a) Yogurt (3.5% fat, 10.0% sucrose) with 1 g woodberry flavor per 1 kg yogurt (b).

	(b) Woodberry flavor	[g]
	benzyl acetate	0.5
	ethyl acetate	4.0
	ethyl 3-methylbutanoate	1.5
5	(Z)-3-hexenol	0.1
	alpha-ionone	0.2
	linalool	0.5
	3-methylbutyl 3-methylbutanoate	0.3
	4-(4-hydroxyphenyl)-2-butanone	2.0
10	cyclopentadecanolide	0.4
	vanillin	0.5
	propylenglycol	90.0

Compared with the blank woodberry flavored yogurt, a strong red fruit note, reminiscent on blackberry, was present. Addition of 3-mercaptoputanoic acid ethyl ester at 2 mg/kg to the blank woodberry flavored yogurt increased the freshness, and the overall flavor profile changed to blueberry. In contrast, an addition of 3-mercaptophexanoic acid methyl ester, i.e. a long chain 3-mercaptopcarboxolic ester as described by Swiss patent 557 423, at 0.2 mg/kg, resulted in a soapy taste profile. At a level of 2 mg 3-mercaptophexanoic acid methyl ester per 1 kg yogurt yielded a fatty-meaty, sulfury aroma profile.

EXAMPLE 7

Comparison of two fragrance accords, either with 3-mercaptoputanoic acid methyl ester or with 3-mercaptophexanoic acid methyl ester

To a clementine accord as described below, 0.004%^(w/w)

- 5 3-mercaptoputanoic acid methyl ester was added. At that level, the accord turned from orange-mandarin to green clementine. The sample with addition of 3-mercaptoputanoic acid methyl ester was more sparkling, natural clementine and strongly increased the diffusivity. When the 3-mercaptophexanoic acid methyl ester was used instead, the diffusivity was
- 10 much less, and a disturbing sulfury, fatty-meaty side note appeared.

Formula of clementine accord:

	rose oxide	1
	buchu leaf oil	2
	geranyl acetate	3
15	geranyl butyrate	3
	ethyl caprylate	4
	(E)-2-hexenale	4
	geranyl isobutyrate	4
	cinnamic aldehyde	5
20	oxane 5% in dipropylene glycol	5
	hexanale	6
	(Z)-3-hexenol	6
	linalool oxyd	6
	isoeugenol acetate	7
25	corps pampelmousse 10%	
	in triethyl citrate	10
	benzaldehyde	15

	allyl hepatanoate	15
	cinnamyl acetate	20
	beta ionone	24
	ethyl acetoacetate	60
5	gamma undecalactone	80
	ethyl acetate	120
	labienoxime	200
	lemon oil italy	600
	furonol 1% in triethyl citrate	1060
10	orange oil 7-fold	2000
	orange oil brasil	2400
	dipropylene glycol	<u>3340</u>
		10000

While the invention has been illustrated and described with respect to illustrative embodiments and modes of practice, it will be apparent to a person skilled in the art that various modifications and improvements may be made without departing from the scope and spirit of the invention. Accordingly, the invention is not to be limited by the illustrative embodiments and practice.

What is claimed is: